REMARKS

Claims 1-26, 29 and 30 are pending in the application and have been rejected under 35 U.S.C. § 112. Claims 6, 8, 10-12, 21, 24, 29, and 30 have been amended as indicated above, and Claims 1-5, 7, 13-20, 22-23 and 25-28 have been cancelled from the application. New Claims 31-33 have been added to the application. Hence, the claims presently under consideration are Claims 6, 8-12, 21, 24 and 29-33. The amendments to the claims and the newly added claims are supported in the application as follows.

Claims 6, 12 and 21 have been amended to specify that the subject is a "Caucasian female subject" rather than a "mammalian subject." To conform their language with Claim 6, from which they now depend, Claims 10 and 11 also have been amended to delete "mammalian." Support for this amendment to Claims 6, 12 and 21 is found throughout the application, for example, in cancelled Claims 19 and 20; at page 5, lines 23-24; at page 23, lines 6-8; and at page 32, lines 21-24. Regarding the recitation of "Caucasian" in amended Claims 6, 12 and 21, the specification at page 23 states that the study population consisted of women living in the Ommoord district of Rotterdam in the Netherlands. As the Netherlands is predominantly Causasian, this disclosure suggests that the women in the study were Caucasian. This suggestion is confirmed by the text at page 32, which states that "the genotype and allele frequencies are similar to those observed in *other* Caucasian study populations..." (emphasis added). By referring to "other Caucasian study populations," the disclosure at page 32 unambiguously, albeit indirectly, discloses that the study group of Example 1 consisted of Caucasian women.

Claims 6, 12 and 21 have been amended to recite that the subject comprises a vitamin D receptor gene having a *Bsm*I site, an *Apa*I site and a *Taq*I site, in which the *Bsm*I site can exist as a B or b allelic form, the *Apa*I site can exist as an A or a allelic form, and the *Taq*I site can exist as a T or t allelic form, and that determining risk of bone fracture includes the step of detecting

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the presence of the baT haplotype for this gene. Claims 6, 12 and 21 also have been amended to indicate that the presence of both the px haplotype of the estrogen receptor α gene and the baT haplotype of the vitamin D receptor indicates an increased susceptibility to bone fracture, and amended further to include a determination of whether these haplotypes are present. Support for these amendments to Claims 6, 12 and 21 are found throughout the specification, for example, in cancelled Claims 3-5, 14-16, 22 and 26, and at page 3, lines 24-31; page 4, lines 7-17; page 5, lines 7-17; page 5, line 31 to page 6, line 3; page 10, lines 21-28; page 11, lines 11-14; page 12, lines 10-13; page 14, line 10 to page 15, line 14; page 20, lines 12-27; page 30, line 20 to page 31, line 8; and page 31, lines 14-16.

Claim 6 also is amended to specify that the subject has at least one estrogen receptor α gene comprising a *PvuII* site and a *XbaI* site, wherein the *PvuII* site can exist as a P or p allelic form, and the *XbaI* site can exist as an X or x alleleic form. This amendment is supported throughout the application, for example, in cancelled Claim 1 and at page 3, lines 13-16; page 4, lines 24-28; page 10, lines 13-16; page 24, lines 4-7; and page 27, lines 12-16.

Claim 12 is further amended to specify that if increased susceptibility to bone fracture is determined as recited in the claim, the treatment will be selected from modifications to lifestyle, exercise, changes in diet, and administration of a suitable drug. Support for this amendment to Claim 12 is found throughout the application, for example, in cancelled Claim 18, and at page 5, lines 21-22; page 6, lines 7-9; page 9, line 32 to page 10, line 2; and at page 15, lines 15-26.

Claims 8, 10, 11 and 24 have been amended to change their dependencies so that they do not depend from cancelled claims. The dependency of Claim 30 has been changed from Claim 29 to Claim 6, in order to better express the intended scope of the invention.

In view of the above remarks, none of the amendments to the claims constitute the addition of new matter to the application.

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Claim Objections

The examiner has objected to Claim 5. However, as Claim 5 has been cancelled from the application, this objection is now moot.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 12-15 have been rejected under this provision because the examiner found it unclear whether these claims referred to a method of treatment or a method of determining susceptibility to bone fracture. Claims 13-15 have been cancelled from the application, hence this ground for rejection is now moot as applied to these claims.

Claim 12, as amended, clearly refers to a method of treatment. Accordingly, the examiner is asked to remove this ground for the rejection of Claim 12.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-26 and 29-30 are rejected for failing to comply with the enablement requirement. Of these, Claims 1-5, 7, 13-20, 22, 23, 25 and 26 have been cancelled from the application, hence this ground for rejection is moot with respect to these claims. Of the claims rejected here under 35 U.S.C. § 112, first paragraph, Claims 6, 8-12, 21, 24 and 29-30 remain under consideration.

As amended, independent Claims 6, 12 and 21 are limited to detecting, treating or formulating a treatment regimen for decreasing bone fracture susceptibility in Caucasian female subjects who carry the p and x haplotype of the estrogen α receptor (ER) gene and also the baT haplotype of the vitamin D receptor (VDR) gene. The examiner appears to find that the correlation between fracture risk and estrogen receptor α (ERα) plus vitamin D receptor (VDR) haplotype is established only in the case of the px + baT haplotype in Caucasian females. In the case of baT, the examiner appears to find that the risk is established only for subjects homozygous for this haplotype (Office Action, page 9, last paragraph).

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Applicants point out that amended Claims 6, 12 and 21 and all claims depending therefrom are directed to determining a combination of the px and baT haplotypes in Caucasian women. It is respectfully submitted that although the highest association with fracture risk of the combined px and baT haplotypes were observed when the latter was homozygous, the specification illustrates that even a combination of a px + baT heterozygote carries a higher risk (compared to a non-baT genotype) of fracture. This is disclosed in the specification, for example, at page 30, lines 11-17. As shown in Figure 4, even for a baT heterozygote, there is a trend to higher risk values over a non-baT reference. In the light of this knowledge, it would be reasonable to formulate or recommend a treatment regimen for any carrier of the baT haplotype present in combination with a px haplotype. Accordingly, the examiner is respectfully requested to withdraw this ground for rejection.

At page 7 of the Office Action, the examiner asserts that the specification teaches only the ERα and VDR haplotypes from humans, and not other mammalian species. The claims as amended now are limited to human subjects, more specifically, female Caucasian subjects. The study population of Example 1 was female Caucasian women, hence this amendment to the claims is commensurate with the disclosure of the application. In view of the foregoing, this concern is believed to have been fully addressed and the examiner therefore is asked to withdraw this ground for rejection.

At pages 10-18 of the Office Action, the examiner proposes that the relationship between the various alleles of the ERα and the VDR genes and susceptibility to bone fracture is unpredictable. These pages include a discussion of several published studies relating the allelic frequencies of the ERα and VDR genes and bone fracture frequencies in various patient populations. However, these published studies are not germane to the patentability of the present claims, especially in view of the amendments to independent Claims 6, 12 and 21. The methods

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now claimed herein are based on the determination of the px haplotype of the ERα gene and the baT haplotype of the VDR gene in Caucasian females, which methods are consistent with the results set forth in Example 1 (pages 23-33).

With regard to the specific documents cited by the examiner, the following response is made:

Aessens *et al*, in relation to VDR, examines only the *Bsm*I allele. The present claims relate to the haplotype formed by the combination of a *Bsm*I site, an *Apa*I site and a *Taq*I site. Accordingly, the results of Aessens *et al* do not have a direct bearing on the predictability of the methods claimed herein.

Kobayashi *et al* relates to a population of non-Caucasian subjects, whereas the present claims relate to methods involving only a Caucasian female population.

VanMeurs *et al* is a publication by some of the present inventors relating to the data of the present application. The present claims are believed to be consistent with the data of the examples, and consistent also with the later publication of VanMeurs *et al*.

Uitterlinden *et al* and Willing *et al* are understood to be cited to indicate that associations between bone fracture risk and gene haplotypes might be due to population effects. The present claims, as amended, refer to only a female Caucasian population, and thus are not inconsistent with these citations.

In view of the foregoing remarks and amendments to the claims, applicants believe they have addressed and overcome all of the examiner's concerns related to unpredictability and other aspects of 35 U.S.C. § 112, paragraph one. Claims 6, 12 and 21, as well as Claims 8-11, 24, 29 and 30 depending therefrom, are believed to be in compliance with 35 U.S.C. § 112, first paragraph, and withdrawal of the rejections under this provision is respectfully requested.

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Rejections under 35 U.S.C. § 102(b)

Claims 1-3, 8-10, 12, 13, 19-20, 25 and 29-30 stand rejected as anticipated by Willing et al. (1998). Of these, Claims 1-3, 13, 19, 20 and 25 have been cancelled from the application, hence this ground for rejection is moot as applied to these claims. The non-cancelled claims rejected over this reference thus are Claims 8-10, 12 and 29-30. Claims 8-10 and 29-30 depend from Claim 6, hence Claim 6 is discussed below.

The examiner describes Willing et al. as teaching the association of bone fracture risk with the *Bsm*I region of VDR and the *Xba*I and *Pvu*I regions of ERα. As amended, independent Claims 6 and 12 rely on identifying and treating bone fracture risk based on the presence in a female Caucasian of the px haplotype of the *Pvu*II and *Xba*I sites of the ERα gene and the baT haplotype of the *Bsm*I, *Apa*I and *Taq*I sites of the VDR gene. Willing *et al* does not teach or remotely suggest analysis of the *Apa*I and *Taq*I polymorphisms of the VDR gene. Claims 6 and 12, as amended, include determination of the allelic forms of VDR at three different restriction sites, i.e., the *Bsm*I, *Apa*I and *Taq*I, whereas Willing et al. teaches the analysis of the allelic forms at only one of these restriction sites. Moreover, Claim 6 recites a step not disclosed by Willig et al., namely, "determining the copy number of a member of the group consisting of the P, p, X and x alleles of the estrogen receptor α gene and the B, b, A, a, T and t alleles of the vitamin D receptor gene." In view of these remarks, it is shown that Willing et al. does not anticipate amended Claims 6 and 12.

The pending dependent claims rejected over this reference, Claims 8-10 and 29-30, incorporate all of the limitations of Claim 6, from which they directly or indirectly depend. Thus, for the reasons given above, Claims 8-10 and 29-30 also are not anticipated by Willing et al.

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In view of the above, the examiner is asked to remove the rejection of Claims 6, 8-10, 12, and 29-30 under 35 U.S.C. § 102(b) over Willing et al.

Rejections under 35 U.S.C. § 103

Claims 4-5, 14-15 and 26 are rejected as being obvious over Willing et al. (1998) in view of Uitterlinden et al. (2001). All of these claims have been cancelled from the application, hence this ground for rejection is now moot.

CONCLUSION

In light of the foregoing amendments and remarks, applicants believe that Claims 6, 8-12, 21, 24 and 29-33 are now in condition for allowance, and notification to this effect is respectfully requested.

Respectfully submitted,

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